ATTACHMENT "A"

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1: Pharm Res. 1995 Mar;12(3):413-20.

A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability.

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A biopharmaceutics drug classification scheme for correlating in vitro drug product dissolution and in vivo bioavailability is proposed based on recognizing that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption. This analysis uses a transport model and human permeability results for estimating in vivo drug absorption to illustrate the primary importance of solubility and permeability on drug absorption. The fundamental parameters which define oral drug absorption in humans resulting from this analysis are discussed and used as a basis for this classification scheme. These Biopharmaceutic Drug Classes are defined as: Case 1. High solubility-high permeability drugs, Case 2. Low solubility-high permeability drugs, Case 3. High solubility-low permeability drugs, and Case 4. Low solubility-low permeability drugs. Based on this classification scheme, suggestions are made for setting standards for in vitro drug dissolution testing methodology which will correlate with the in vivo process. This methodology must be based on the physiological and physical chemical properties controlling drug absorption. This analysis points out conditions under which no in vitro-in vivo correlation may be expected e.g. rapidly dissolving low permeability drugs. Furthermore, it is suggested for example that for very rapidly dissolving high solubility drugs, e.g. 85% dissolution in less than 15 minutes, a simple one point dissolution test, is all that may be needed to insure bioavailability. For slowly dissolving drugs a dissolution profile is required with multiple time points in systems which would include low pH, physiological pH, and surfactants and the in vitro conditions should mimic the in vivo processes.(ABSTRACT TRUNCATED AT 250 WORDS)

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